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## **Steroid Use in Crohn's Disease**

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**Short title:** Steroid use in IBD

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**ABSTRACT**

The incidence and prevalence of Crohn's disease is increasing, particularly in the Western world and Asia. Corticosteroids have been used for decades to treat active Crohn's disease and remain the mainstay in management of moderate-to severe relapses in Crohn's disease. Use of corticosteroids, despite their efficacy, may be associated with several drawbacks. This review article provides a comprehensive account of the role of corticosteroids in inducing remission in adult patients with Crohn's disease including aspects such as approaches to steroid-sparing and to minimize the risk of steroid dependency, as well as the role of newer corticosteroids such as budesonide in reducing systemic side effects.

## INTRODUCTION

Crohn's disease (CD) is a life-long chronic inflammatory condition, which is characterized by repetitive flares and periods of inactive disease. Its relapsing behaviour frequently necessitates a combination of approaches to effectively treat active disease. In clinical practice, active CD is defined by the presence of symptoms such as chronic or nocturnal diarrhea, abdominal pain, and rectal bleeding (1); in clinical trials disease activity is measured by a CD Activity Index (CDAI) score  $\geq 150$  (2, 3). One challenging goal in the therapy of CD flares is to induce remission in active CD. Several agents are available for induction of remission of CD, such as corticosteroids and anti-tumor necrosis factor (TNF) antibodies (4). The selection of an optimal treatment depends on several factors, including severity of disease, location, previous response to therapy, and co-morbidities.

Historically, prior to the advent of biologic therapies, corticosteroids had been the most effective class of medication for treatment of acute flares of CD in adults (5) and children (6). Corticosteroids down-regulate the transcription of genes involved in pro-inflammatory cytokine production such as interleukin (IL)-1, IL-6, and NF- $\kappa$ B, and TNF and inhibit the expression of adhesion molecules in inflamed tissues and the trafficking of activated immune cells (7-9). Corticosteroids have been used for the treatment of inflammatory bowel disease since the 1950s (10). In a pivotal trial Truelove and Witts showed that oral cortisone at a dose of 100 mg daily effectively induced remission in patients with active ulcerative colitis (10). In patients with CD, corticosteroids are used to induce remission in moderate-to-severe ileo-colonic disease, extensive small bowel disease and pure colonic disease (11). Response to corticosteroids has been defined in several clinical studies as clinical improvement after treatment with high-dose oral corticosteroids (usually 40-60mg prednisone/d) within 30 days or clinical improvement after treatment with high-dose intravenous corticosteroids within 7-10 days (4, 12, 13). Conversely, patients who fail to respond to corticosteroids within this timeframe have been defined as corticosteroid refractory or corticosteroid resistant (4). Patients, who initially respond to corticosteroids but

then relapse with corticosteroid tapering or shortly after corticosteroid discontinuation and require reinstitution of corticosteroid therapy at doses of 10-30mg/d to maintain symptom control have been defined as corticosteroid dependent (4, 12). More than 50% of patients treated acutely with corticosteroids will become steroid dependent or steroid resistant (13-17), particularly smokers, or those with colonic disease (18).

Corticosteroids are characterized by several serious side effects that limit their use in the short and long term. Side effects can be classified as early, due to prolonged use or due to abrupt withdrawal (11), and daily use for more than 2-3 weeks significantly increases the risk of adverse events (19). The most common reported side effects are acne, arterial hypertension, hirsutism, striae, moon face, ecchymoses, cataracts, glaucoma, suppression of the adrenal function and infection (mainly increased risk of abdominal and pelvic abscess in CD patients) (1, 15, 20-22). Additionally, corticosteroids can induce a loss of bone mineral density and increase the risk of fractures (23-25). Owing to this significantly increased risk of osteoporosis, whenever corticosteroids are used in IBD patients, an initial baseline DEXA scan as well as supplementation of calcium and vitamin D are warranted once corticosteroid therapy is initiated (26-28). Other side effects which are associated include hyperlipidemia, hypokalemia, hyperglycemia and hypocalcemia (29, 30). In a multivariate analysis by Lichtenstein et al (31), the use of prednisone was associated with an increased risk of infection (OR 2.21, 95% CI 1.46-3.34,  $p < 0.001$ ) and mortality (OR 2.10, 95% CI 1.15-3.83;  $p = 0.016$ ). Therefore, it is important to weight the risk-benefit ratio before use. In clinical practice, steroid-free remission represents an important primary end point in the treatment of CD patients.

This review article focuses on the role of corticosteroids in inducing remission in adult patients with CD. It contains aspects such as approaches to steroid-sparing and minimizing the risk of steroid dependency, as well as the role of newer corticosteroids such as budesonide in reducing systemic side effects.

A literature search matching terms “prednisone”, “prednisolone”, “6-methylprednisolone”, and “budesonide” with the term “Crohn’s disease” was performed in the PubMed, Medline, the Cochrane Central Register of Controlled Trials, and EMBASE database. All relevant articles published in English and German between September 1960 and September 2013 were reviewed.

## Conventional Corticosteroids

### a) Induction of Remission

Conventional corticosteroids, such as prednisone, prednisolone, and 6-methylprednisolone, are highly effective at inducing clinical remission in active CD (1, 15, 21) and are perceived as the most effective therapeutic option for inducing remission of mild to moderate CD. They can induce clinical remission in moderate-to-severe ileocaecal, colonic or small bowel CD as well as in oesophageal and gastric localizations in combination with proton pump inhibitors (4). For an overview of all randomized, double-blind placebo-controlled trials please see **Table 1**. In a study by Summers et al (21), 162 patients with active CD (defined by a Crohn’s Disease Activity Index (CDAI) between 150 - 450) were randomized to receive placebo or prednisone (0.5-0.75mg/kg/day). Clinical remission with a CDAI < 150 was achieved at week 17 in 47% (40/85) in the patients receiving prednisone as compared to 26% (20/70) of patients receiving placebo (NNT=3).

Malchow et al. included 223 patients (110 on placebo, 113 on 6-methylprednisolone 48mg/d) (15). After 1 week of methylprednisolone, the dose was gradually tapered to 12mg/d or placebo. The cycle of steroid treatment was repeated if remission was not achieved by week 6 and 12. At week 18, the percentage of patients in clinical remission (CDAI < 150) was 83% and 37.9 %, respectively, for steroid treatment and placebo (NNT=2).

In a third study, Brignola et al treated 18 patients with methylprednisolone 0.25mg/kg/d or placebo (32). At 6 months, a relapse rate of 78% was observed in the placebo group as

compared to 11% relapse rate in the methylprednisolone group. Several studies compared the benefit of corticosteroids over 5-ASA medications for induction of remission. The two early studies by Summers et al (using sulfasalazine at the equivalent of 2g/d of 5-ASA) and Malchow et al (using sulfasalazine at the equivalent of 1.2g/d of 5-ASA) had both 5-ASA arms in their study protocol (15, 21). At lower 5-ASA concentrations corticosteroids revealed a clear benefit over 5-ASA therapy (15, 21, 33, 34). Studies comparing corticosteroids and higher doses of 5-ASA (3 to 4.5 g/d) did not show a benefit of corticosteroids, although long-term follow-up was not available (34-37).

Corticosteroids are important drugs in inducing clinical remission. They also have a limited capacity to induce mucosal healing or at least endoscopic improvement. Two studies showed a 29% rate of endoscopic remission with corticosteroid therapy (38, 39). Similarly, limited efficacy has been shown in patients with complicated CD. The presence of structuring and penetrating disease is likely to respond poorly to corticosteroids (16). Their use in cases of fistulizing disease is also limited due to evidence of an increased need for surgery (40, 41) and death occurring due to septic complications (15).

No appropriate dose-ranging studies have been performed to evaluate steroid dosing or dose schedules for CD. Comparable clinical effects have been reported from placebo-controlled and active-comparator trials with approximately 50-70% of patients achieving a clinical remission over 8-17 weeks receiving the equivalent of prednisone, 0.5-0.75 mg/kg (or 40 mg/d) daily (21, 42-44). Higher doses of prednisone (1 mg/kg/d) or methyl prednisolone (1mg/kg/d) have demonstrated slightly higher response rates of 80-90% (15, 38). Several studies have also studied dexamethasone and betamethasone in CD patients, but this will not be the main focus of this review (45-47).

## **b) Maintenance of Remission**

Conventional corticosteroids are not indicated for maintaining remission of CD due to their lack of efficacy and the potential multitude of systemic side effects (2). One small study



reported methylprednisolone to be more beneficial than placebo at maintaining remission (32). This result could not be reproduced in two larger studies and one smaller study comparing prednisone and 6-methylprednisolone with placebo (15, 21, 48). The study by Summers et al. (The National Cooperative Crohn's Disease Study) reported that 0.25mg/kg/day was not effective at a 2-year follow-up at preventing relapses among patients in remission (21). The study by Malchow et al. (the European Cooperative Crohn's Disease Study) determined that 6-methylprednisolone 48mg/d once daily was not better than placebo at maintaining remission at 2 years (15). In the study by Smith and colleagues from Cardiff, Wales, prednisone 7.5 mg/d or placebo was given to 64 CD patients with no beneficial effect regarding clinical relapse (48). In summary, a Cochrane Database Review concluded that conventional corticosteroids were not an effective maintenance therapy for up to 2 years (49). Therefore, long-term use of corticosteroids should be avoided and an introduction of steroid-sparing agents such as azathioprine or 6-mercaptopurine should be favoured (50-52).

## **Non-systemic Corticosteroids (Budesonide)**

### **a) Induction of Remission**

More recently, topically-active formulations of corticosteroids such as budesonide have been developed in order to reduce systematic availability and adverse events while maintaining efficacy. Budesonide is a locally acting, topically delivered corticosteroid that undergoes extensive first-pass hepatic metabolism (80-90%) and accordingly, has low systemic absorption (53). Thus, the benefits of corticosteroids in managing mild to moderate CD can be achieved with a reduced risk of systemic adverse effects. Both, the ECCO and the AGA recommend budesonide as a first-line therapy for mild to moderate CD of the ileum and proximal colon (4, 26). For patients with CD, two formulations that target the ileocaecal tract have been formulated: pH-dependent (Budenofalk ® or Budeson ® - Dr. Falk Pharma, Freiburg, Germany) and controlled ileal release (Entocort ® - Astra Zeneca). The current literature is summarized in **Table 2**.

**Budesonide vs. placebo:** Several studies have been published on induction of remission of CD with budesonide. The two main studies showing the superiority of budesonide compared to placebo and inducing clinical remission in patients with active luminal disease are the ones by Greenberg et al. and Tremaine et al. (54, 55). Both trials included patients with terminal ileal, ileocolonic, or right-sided colonic CD. Greenberg et al. reported that budesonide 9 mg/day for 8 weeks was significantly more effective than placebo at induction of remission in active CD (51 % vs. 20 %, respectively,  $p < 0.001$ ) (54). Tremaine et al. found that budesonide 9 mg/day for 8 weeks resulted in remission in 48% of active CD patients but was not significantly different from placebo due to a high remission rate of 33% in the placebo-treated patients ( $p < 0.05$ ) (55). When those two trials were summarized in a metaanalysis, a clear statistically significant effect in favour of budesonide could be found with a NNT=5 (Budesonide achieving remission in one patient) (56).

**Budesonide vs. corticosteroids:** Further 8 RCTs have compared the efficacy of budesonide with oral systemic corticosteroids or beclomethasone dipropionate. All trials recruited patients with distal ileal, ileocecal, or right-sided colonic CD, but most did not report exact patient numbers according to disease location. The remission rates in these studies were 51-60 % in the budesonide group and 52-89 % in the corticosteroid group (42, 43, 57-62). The results of these trials have been summarized in two Cochrane Reviews and show that budesonide is comparable to prednisone in inducing clinical remission in patients with ileo-colonic CD (63, 64).

**Budesonide vs. 5-ASA:** Only one study reported on induction of remission of budesonide vs. mesalazine. In this study, budesonide 9mg/d was a more effective induction therapy than mesalazine 4 g/d (65). A meta-analysis showed that budesonide induces more frequently remission than placebo or 5-aminosalicylic acid with an odds ratio of 1.85 in favour of budesonide vs. placebo (66).

Mantzaris et al. found that endoscopic remission was achieved in only 24% of patients administered budesonide compared to 83% administered with azathioprine ( $p<0.01$ ), indicating that immunomodulators are more effective than budesonide in achieving mucosal healing (67).

Thus, budesonide is safe and effective as an induction therapy for mild to moderate CD involving the terminal ileum and the proximal colon.

### **b) Maintenance of Remission**

Budesonide is superior to placebo for CD remission and it is well tolerated even if it is taken for up to 1 year (68). However, budesonide is not prolonging the time to relapse in CD patients. This has been investigated in several studies, summarized in **Table 3**.

Budesonide is not the drug of choice for maintenance of remission. This observation is based on a pooled analysis of five trials (69-73). All trials evaluated patients with quiescent luminal disease at 52 weeks. Those five trials have been summarized in a systematic review and meta-analysis (56). No statistically significant difference could be detected between budesonide and placebo in terms of prevention of relapse ( $RR=0.93$ ; 95% CI 0.83-1.04). Similar results were published in a Cochrane study (34) and in a meta-analysis (74).

In summary, budesonide is not significantly more effective than placebo (34, 54, 70-73, 75-77) or systemic corticosteroids (78) in maintaining clinical remission in CD.

### **Other agents**

Two additional substances should be mentioned only briefly as those were not the scope of this review. One is a novel formulation of budesonide which has recently been developed. It uses the multimatrix delivery system (MMX®), a special drug-release system characterized by a pH-dependent hydrophilic and inert matrix that acts as a gastroprotective layer, allowing release of the drug only when pH rises above 7. Therefore, it targets the entire colon and

could be used in colonic CD (79-81). The second agent is beclomethasone dipropionate (BDP). It is a topical-acting corticosteroid that is administered as a pro-drug with a rapid first-pass effect (82). Only limited data is available. One study showed superiority of budesonide over BDP with remission rates at 8 weeks of 86.6% vs. 66.6% ( $p < 0.001$ ) (62).

### **Approaches to Steroid-Sparing and Minimizing the Risk of Steroid Dependency**

**Azathioprine and 6-mercaptopurine.** 6-mercaptopurine and its pro-drug azathioprine are purine analogues that competitively interfere with nucleic acid metabolism by acting as substrate competitive antagonists for the hypoxanthine-guanine phosphoribosyl-transferase enzyme (83). Consequently both drugs have immune modifier properties by reducing the cell proliferation. Both drugs have been used successfully to treat patients with active, steroid-refractory, and steroid-dependent inflammatory Crohn's disease, and patients with fistulizing Crohn's disease (84). In some azathioprine and 6-mercaptopurine studies steroid sparing effect of therapy was a primary outcome (85-89). It was assessed variously as (i) the ability to follow pre-defined steroid tapering regimen, and (ii) as the ability to reduce steroid dose to  $< 10$  mg/day while maintaining remission. In the five studies reporting data on reduction of steroid consumption patients with active disease who received antimetabolite reduced their steroid consumption more significantly compared to placebo (85-88, 90). In a meta-analysis the pooled OR was 3.69 (95% CI 2.12-6.42) indicating a significant steroid sparing effect (84). The NNT to obtain a steroid sparing effect in one patient was 3.

**Anti-TNF-antibodies.** In ACCENT I, 25 % of the patients who received 5mg/kg of infliximab and 34% of patients who received 10 mg/kg of infliximab were able to completely discontinue steroid therapy altogether and remain in remission (91). In the CHARM trial, 35% of the randomized responders who received adalimumab 40mg every other week were off steroid therapy and in remission at week 26 compared to only 3 % of placebo patients ( $p < 0.001$ ). At week 56, 29 % of patients who received adalimumab 40mg every other week

were in remission off steroids compared to only 6 % of placebo-treated patients ( $p=0.008$ ) (92). No comparable studies exist on certolizumab pegol.

As mentioned above, over 50 % of patients become steroid-dependent or undergo surgery within one year of commencing therapy (14). Immunosuppressives and anti-TNF-antibodies can reduce corticosteroid dependency and maintain disease remission and should therefore be considered early in the therapy.

### **SUMMARY AND PRACTICAL TIPS**

Based on the NICE clinical guidelines, published in 2012, we will offer best practice advice on the care of patients with Crohn's disease (93). Because corticosteroids are rapidly active and highly effective, they remain the mainstay for the induction of clinical remission of CD. If one needs to start with corticosteroids, use 0.5-0.75 mg/kg (or 40 mg/d) daily (21, 42-44). Offer whenever possible monotherapy with glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission especially in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period (93). In people with one or more of distal ileal, ileocecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain to the patient however, that budesonide is less effective than a conventional glucocorticosteroid, but may have fewer side effects (93).

Obviously, there is an increased concern about adverse effects associated with long-term conventional corticosteroid use, including suppression of the adrenal axis. Thus, clinicians must always consider a quick tapering of the dose and adverse events when using an

appropriate maintenance therapy. When a clinical response has been achieved, doses are tapered according to the rapidity and completeness of response. Generally, doses are tapered by 5-10 mg/week until 20 mg and then by 2.5-5 mg/week until discontinuation of therapy. In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that 5-ASA is less effective than a conventional glucocorticosteroid or budesonide, but may have fewer side effects than a conventional glucocorticosteroid (93). But always remember: do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations (93).

In summary: within the changing landscape of available treatments in Crohn's disease, glucocorticosteroids still remain an important therapy regardless of short- and long-term side effects.

#### Key Point Summary:

- For induction of remission with glucocorticosteroids in a CD flare start with corticosteroids 0.5-0.75 mg/kg (or 40 mg/d) daily
- Due to short- and long-term side effects of glucocorticosteroids quick tapering is recommended (e.g. 5-10 mg/week until 20 mg and then by 2.5-5 mg/week until discontinuation of therapy)
- Topically-active formulations of corticosteroids such as budesonide should be used in mild and moderate flares.

Title for tables:

Table 1: Overview of randomized controlled trials of conventional corticosteroids in the treatment for Crohn's disease.

Table 2: Overview of randomized double-blind controlled trials of budesonide in induction of remission for Crohn's disease.

Table 3: Overview of randomized double-blind controlled trials of budesonide in maintenance of remission for Crohn's disease.

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Reference	Year	Type of study	Total number of patients	Drugs administered	Study population	Duration of Study (Weeks)	Primary end point	Remission rate %	p-value
<b>Corticosteroids vs. placebo</b>									
Summers <sup>19</sup>	1979	pc RCT	162 (77 placebo, 85 prednisone)	(1) prednisone 0.25mg/kg/d (up to 0.75 mg/kg/d)  (2) sulfasalazine 1g/15kg to a max of 5g/d  (3) AZA  (4) placebo	CD patients followed by the National Cooperative Crohn's Disease Study (NCCDS), USA; 14 sites	12 months	clinical remission (CDAI<150)	Prednisone 47% (40/85) remission, placebo 26% (20/77) remission at week 17	0.0004
Malchow <sup>15</sup>	1984	RCT, placebo	105 (58 placebo, 47 6-methylprednsione)	(1) 6-methylprednisone 48mg/d (tapered over 6 weeks)  (2) sulfasalazine 3g/d  (3) combination sulfasalazine plus corticosteroids  (4) placebo	CD patients followed by the European Cooperative Crohn's Disease Study (ECCDS), Europe, 15 sites	24 months	clinical remission (CDAI<150)	Prednisone 83% (39/47) remission, placebo 37.9% (22/58) at week 18	<0.001
Brignola <sup>30</sup>	1988	RCT, placebo	18 (9 placebo, 9 methylprednisolone)	methylprednisolone 0.25mg/kg/d	CD patients, single center	6 months	Relapse rate (CDAI increase of > 100 and over 150 for 2 >weeks)	Methylprednisone 11% relapse (1/9), placebo 78% relapse (7/9)	n.a.
<b>Corticosteroids vs. 5-ASA</b>									
Scholmerich	1990	db RCT	62 (30 mesalazine, 32 6-	(1) 6-methylprednisolone	CD patients, Germany and	24 weeks	insufficient efficacy (fever > 39°C over six	(1) Methylprednisolone	n.a.

<sup>31</sup>			methylprednisolone)	48mg/d tapered over 24 weeks ( 2) mesalazine 2g/day for 24 weeks	Austria		days, increase CDAI > 350, increase CDAI>50 points since last visit, decrease of CDAI of less than 60 points and van Hees Index < 30 points at week 4, or CDAI > 150 and van Hees Index > 200 at week 12	65.5% (21/32) (2) mesalazine 26.7% (8/30)	
Martin <sup>34</sup>	1990	RCT	50 (28 prednisone, 22 mesalamine)	(1) oral prednisone 40 mg/d for 2 weeks followed by a 4mg/d weekly reduction for a total of 12 weeks  (2) Mesalamine 1g 3x/d for 12 weeks	CD patients, Canada, 8 sites	12 weeks	clinical remission (CDAI<150)	(1) prednisone 42.8% (12/28) (2) mesalamine 40.9% (9/22)	n.s.
Gross <sup>33</sup>	1995	mc, dd RCT	31 (16 6-methylprednisolone, 15 mesalamine)	(1) 6-methylprednisolone 48mg/d tapered over 8 weeks  (2) mesalazine 1.5g 3x/day for 8 weeks	CD patients , Germany	8 weeks	clinical remission (CDAI<150)	(1) 6-methylprednisolone 56.7% (9/16) (2) mesalazine 40% (6/15)	0.5867
Prantera <sup>35</sup>	1999	db, dd,	94 (31 6-methylprednisolone, 35 mesalamine, 28 mesalamine microgranular coated with Eudragit S)	(1) oral 6-methylprednisolone 40mg/d in three doses, then tapered by 4mg/d every week for 12 weeks  (2) mesalamine 4g/d in three doses for 12	CD patients, Italy, 14 sites	12 weeks	clinical remission (CDAI<150)	(1) 6-methylprednisolone 61 % (19/31) (2) mesalazine tablet 60% (21/35) (3) mesalazine granules 79% (22/28)	n.s.

				weeks  (3) mesalamine microgranules coated with Eudragit 4g/day in three doses/d for 12 weeks					
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pc= placebo controlled, RCT= randomized controlled trial, db= double-blind, mc= multi-center, dd= double-dummy

Reference	Year	Type of study	Total number of patients	Drugs administered	Study population	Duration of Study (Weeks)	Primary end point	Remission rate %	p-value
<b>budesonide vs. placebo</b>									
Greenberg <sup>53</sup>	1994	db, pc RCT	258	(1) Budesonide 3mg (67) (2) 9mg (61) (3) 15mg (64) (4) placebo (66)	active CD, Canada, 27 sites	8	clinical remission (CDAI<150)	(1) 33 (2) 51 (3) 43 (4) 20	(1) 0.13 (2) < 0.001 (3) 0.009
Tremaine <sup>54</sup>	2002	db, pc, RCT	200	(1) Bud 4.5mg 2x/d 80 (2) Bud 9mg 1x/d (79) (3) placebo (41)	mild-to-moderate CD (CDAI 200-450), USA, 24 sites	8	clinical remission (CDAI<150)	(1) 53 (2) 48 (3) 33	< 0.05
<b>budesonide vs. corticosteroid</b>									
Rutgeerts <sup>41</sup>	1994	db, pc, RCT	176	(1) Bud 9 mg for 8 weeks, then 6mg for 2 weeks (88) (2) Prednisolone 40 mg for 2 weeks, 30mg for 2 weeks, 25 mg for 2 weeks, then taper by 5mg/week (88)	active ileal or ileocecal CD, Europe, 11 sites	10	clinical remission (CDAI<150)	(1) 53 (2) 66	0.12
van Ierssel <sup>58</sup>	1995	db, dd, RT	18	(1) Bud 9 mg for 8 weeks, then 6mg for 2 weeks (9) (2) Prednisolone 40 mg for 2 weeks, then taper by 5mg/week (9)	active CD, Holland, 1 site	10	effect on peripheral blood NK activity	(1) 56 (2) 89	n.a.

[illegible]



Thomsen <sup>64</sup>	1998	db RCT	182	(1) Bud 9 mg/d (93) (2) mesalamine 2x 2g/d (89)	active CD (CDAI 200-400), Europe, South Africa, Australia, 25 sites	16	clinical remission (CDAI < 150)	(1) 62 (2) 36	< 0.001
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db=double-blind, pc= placebo-controlled, RCT= randomized controlled trial, dd= double-dummy

Reference	Year	Type of study	Total number of patients	Drugs administered (n)	Study population	Duration of Study (Weeks)	Primary end point	Remission rate %	p-value
<b>budesonide vs. placebo</b>									
Greenberg <sup>67</sup>	1996	db RCT	105	(1) Bud 3mg/d (33) (2) Bud 6 mg/d (36) (3) placebo (36)	Canada, 23 sites	52	maintenance of remission, relapse defined as CDAI remaining at > 150 and a minimum increase of 60 points	Relapse rate (1) 70% (2) 61% (3) 67%	0.75
Lofberg <sup>68</sup>	1996	db RCT	90	(1) Bud 3mg/d (31) (2) Bud 6 mg/d (32) (3) placebo (27)	Europe, 11 sites	52	maintenance of remission, relapse defined as CDAI remaining at > 150 and a minimum increase of 60 points from entry	Relapse rate (1) 74% (2) 59% (3) 63%	0.44
Ferguson <sup>70</sup>	1998	db RCT	75	(1) Bud 3mg/d(26) (2) Bud 6 mg/d (22) (3) placebo (27)	Europe and Australie, 20 sites	52	maintenance of remission, relapse defined as CDAI remaining at > 150 and a minimum increase of 60 points from entry	Relapse rate (1) 46% (2) 48% (3) 60%	n.s.
Gross <sup>69</sup>	1998	db, RCT	179	(1) Bud 3 mg/d (84) (2) placebo (95)	Germany, 8 sites	52	maintenance of remission, relapse defined as CDAI remaining at > 150	Relapse rate (1) 67% (56/84) (2) 65% (62/95)	n.s.
Hanauer <sup>71</sup>	2005	db, pc RCT	110	(1) Bud 6mg/d (54) (2) placebo (54)	USA, 22 sites	52	time to relapse (CDAI > 150 plus increase of at least 60 points)	Median time to relapse	0.132

								(1) 360 days	
								(2) 169 days	

db= double-blind, RCT= randomized controlled trial, pc= placebo-controlled